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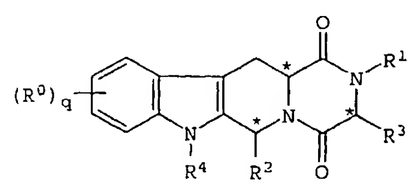
(54) DERIVES PYRAZINO 1',2':1,6 PYRIDO 3,4-B INDOLE1,4-DIONE

(54) PYRAZINO 1',2':1,6 PYRIDO 3,4-B INDOLE1,4-DIONE DERIVATIVES

(57)
Compounds of the general structural formula (I), and use of the compounds and salts and solvates thereof, as thereapeutic agents. In particular, the invention relates to compounds that are potent and selective inhibitors of cyclic guanosine 3', 5'-monophosphate specific phosphodiesterase (cGMP- specific PDE), in particular PDE5, and have utility in a variety of therapeutic areas wherein such inhibition is considered beneficial, including the treatment of cardiovascular disorders and erectile dysfunction.



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(54) Titre : DERIVES PYRAZINO 1',2':1,6 PYRIDO 3,4-B INDOLE1,4-DIONE

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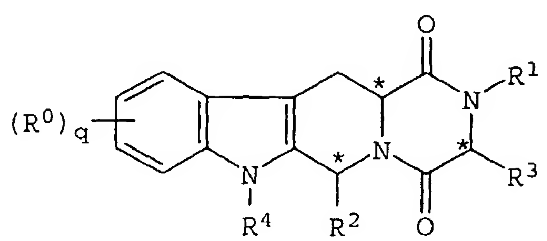

(I)

(57) Abrégé/Abstract:

Compounds of the general structural formula (I), and use of the compounds and salts and solvates thereof, as thereapeutic agents. In particular, the invention relates to compounds that are potent and selective inhibitors of cyclic guanosine 3', 5'-monophosphate specific phosphodiesterase (cGMP-specific PDE), in particular PDE5, and have utility in a variety of therapeutic areas wherein such inhibition is considered beneficial, including the treatment of cardiovascular disorders and erectile dysfunction.

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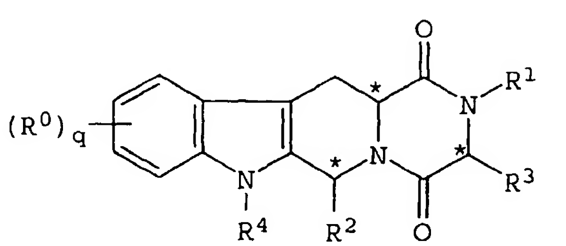
(54) Title: PYRAZINO 1',2':1,6 PYRIDO 3,4-B INDOLE1,4-DIONE DERIVATIVES



(I)

(57) Abstract: Compounds of the general structural formula (I), and use of the compounds and salts and solvates thereof, as therapeutic agents. In particular, the invention relates to compounds that are potent and selective inhibitors of cyclic guanosine 3', 5'-monophosphate specific phosphodiesterase (cGMP-specific PDE), in particular PDE5, and have utility in a variety of therapeutic areas wherein such inhibition is considered beneficial, including the treatment of cardiovascular disorders and erectile dysfunction.

WO 02/098877 A1

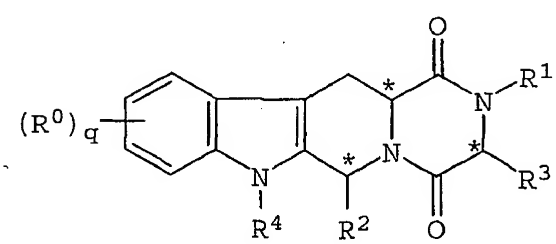
PYRAZINO'1',2':1,6!PYRIDO'3,4-B!INDOLE1,4-DIONE DERIVATIVES

FIELD AND BACKGROUND OF THE INVENTION

This invention relates to a series of compounds, to methods of preparing the compounds, to pharmaceutical compositions containing the compounds, and to their use as therapeutic agents. In particular, the invention relates to compounds that are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP-specific PDE), in particular PDE5, and have utility in a variety of therapeutic areas wherein such inhibition is considered beneficial, including the treatment of cardiovascular disorders and erectile dysfunction.

SUMMARY OF THE INVENTION

The present invention provides compounds of formula (I)

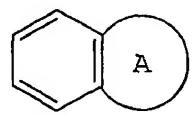


(I)

wherein R^0, independently, is selected from the group consisting of halo and C_{1-6}alkyl;

R^1 is selected from the group consisting of hydro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}-alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, aryl-C_{1-3}alkyl, C_{1-3}alkylenearyl, and heteroarylC_{1-3}alkyl;

R^2 is selected from the group consisting of an optionally substituted monocyclic aromatic ring selected from the group consisting of benzene, thiophene, furan, and pyridine, and an optionally substituted bicyclic ring



wherein the fused ring A is a 5- or 6-membered ring, saturated or partially or fully unsaturated, and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulfur, and nitrogen;

R^3 is selected from the group consisting of hydro and C_{1-6}alkyl,

or R^1 and R^3 together form a 3- or 4-membered alkyl or alkenyl chain component of a 5- or 6-membered ring;

R^4 is selected from the group consisting of C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}heterocycloalkyl, C_{2-6}-alkenyl, C_{1-3}alkylenearyl, arylC_{1-3}alkyl, heteroaryl-C_{1-3}alkyl, $C(=O)R^a$, aryl, heteroaryl, $C(=O)OR^a$, $C(=O)$-NR^aR^b, $C(=S)NR^aR^b$, SO_2R^a, SO_2OR^a, $SO_2NR^aR^b$, $S(=O)R^a$, $S(=O)NR^aR^b$, $C(=O)NR^aC_{1-4}$alkyleneOR^a, $C(=O)NR^aC_{1-4}$alkyleneHet, $C(=O)C_{1-4}$alkylenearyl, $C(=O)C_{1-4}$alkyleneheteroaryl, C_{1-4}alkylenearyl substituted with one or more

of $SO_2NR^aR^b$, NR^aR^b, $C(=O)OR^a$, $NR^aSO_2CF_3$, CN, NO_2, $C(=O)R^a$, OR^a, C_{1-4}alkyleneNR^aR^b, and OC_{1-4}alkyleneNR^aR^b, C_{1-4}alkyleneHet, C_{1-4}alkylene$C(=O)C_{1-4}$alkylenearyl, C_{1-4}alkylene$C(=O)C_{1-4}$alkyleneheteroaryl, C_{1-4}alkylene-$C(=O)$Het, C_{1-4}alkylene$C(=O)NR^aR^b$, C_{1-4}alkyleneOR^a, C_{1-4}alkylene$NR^aC(=O)R^a$, C_{1-4}alkyleneOC_{1-4}alkyleneOR^a, C_{1-4}alkyleneNR^aR^b, C_{1-4}alkylene$C(=O)OR^a$, and C_{1-4}alkyleneOC$_{1-4}$alkylene$C(=O)OR^a$;

Het represents a 5- or 6-membered heterocyclic ring, saturated or partially or fully unsaturated, containing at least one heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur, and optionally substituted with C_{1-4}alkyl or $C(=O)OR^a$;

R^a is selected from the group consisting of hydro, C_{1-6}alkyl, aryl, arylC_{1-3}alkyl, C_{1-3}alkylenearyl, heteroaryl, heteroarylC_{1-3}alkyl, and C_{1-3}alkyleneheteroaryl;

R^b is selected from the group consisting of hydro, C_{1-6}alkyl, aryl, heteroaryl, arylC_{1-3}alkyl, heteroarylC_{1-3}alkyl, C_{1-3}alkylene$N(R^a)_2$, C_{1-3}alkylenearyl, C_{1-3}alkyleneHet, haloC_{1-3}alkyl, C_{3-8}cycloalkyl, C_{3-8}heterocycloalkyl, C_{1-3}alkyleneheteroaryl, C_{1-3}-alkylene$C(=O)OR^a$, and C_{1-3}alkyleneC_{3-8}heterocycloalkyl;

or R^a and R^b are taken together to form a 5- or 6-membered ring, optionally containing at least one heteroatom;

q is 0, 1, 2, 3, or 4; and

pharmaceutically acceptable salts and hydrates thereof.

As used herein, the term "alkyl" includes straight chained and branched hydrocarbon groups containing the indicated number of carbon atoms,

typically methyl, ethyl, and straight chain and branched propyl and butyl groups. The hydrocarbon group can contain up to 16 carbon atoms. The term "alkyl" includes "bridged alkyl," e.g., a C_6-C_{16} bicyclic or polycyclic hydrocarbon group, for example, norbornyl, adamantyl, bicyclo[2.2.2]octyl, bicyclo[2.2.1]heptyl, bicyclo[3.2.1]octyl, and decahydronaphthyl." The term "cycloalkyl" is defined as a cyclic C_3-C_8 hydrocarbon group, e.g., cyclopropyl, cyclobutyl, cyclohexyl, and cyclopentyl.

The terms "alkenyl" and "alkynyl" are defined identically as "alkyl," except for containing a carbon-carbon double bond or carbon-carbon triple bond, respectively. "Cycloalkenyl" is defined similarly to cycloalkyl, except a carbon-carbon double bond is present in the ring.

The term "alkylene" refers to an alkyl group having a substituent. For example, the term "C_{1-3}alkylenearyl" refers to an alkyl group containing one to three carbon atoms, and substituted with an aryl group.

The term "halo" or "halogen" is defined herein to include fluorine, bromine, chlorine, and iodine.

The term "haloalkyl" is defined herein as an alkyl group substituted with one or more halo substituents, either fluoro, chloro, bromo, or iodo. Similarly, "halocycloalkyl" is defined as a cycloalkyl group having one or more halo substituents.

The term "aryl," alone or in combination, is defined herein as a monocyclic or polycyclic aromatic group, preferably a monocyclic or bicyclic aromatic group, e.g., phenyl or naphthyl. Unless

otherwise indicated, an "aryl" group can be unsubstituted or substituted, for example, with one or more, and in particular one to three, halo, alkyl, hydroxy, $C(=O)OR^a$, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkoxy, cyano, nitro, amino, alkylamino, acylamino, alkylthio, alkylsulfinyl, and alkylsulfonyl. Exemplary aryl groups include phenyl, naphthyl, tetrahydronaphthyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methylphenyl, 4-methoxyphenyl, 3-trifluoromethylphenyl, 4-nitrophenyl, and the like. The terms "arylC_{1-3}alkyl" and "heteroarylC_{1-3}alkyl" are defined as an aryl or heteroaryl group having a C_{1-3}alkyl substituent.

The term "heteroaryl" is defined herein as a monocyclic or bicyclic ring system containing one or two aromatic rings and containing at least one nitrogen, oxygen, or sulfur atom in an aromatic ring, and which can be unsubstituted or substituted, for example, with one or more, and in particular one to three, substituents, like halo, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkyl, nitro, amino, alkylamino, acylamino, alkylthio, alkylsulfinyl, and alkylsulfonyl. Examples of heteroaryl groups include thienyl, furyl, pyridyl, oxazolyl, quinolyl, isoquinolyl, indolyl, triazolyl, isothiazolyl, isoxazolyl, imidizolyl, benzothiazolyl, pyrazinyl, pyrimidinyl, thiazolyl, and thiadiazolyl.

The term "Het" is defined as monocyclic, bicyclic, and tricyclic groups containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur. A "Het" group also can contain an oxo group (=O) attached to the ring. Nonlimiting examples of Het groups include 1,3-

dioxolanyl, 2-pyrazolinyl, pyrazolidinyl, pyrrolidinyl, piperazinyl, a pyrrolinyl, 2H-pyranyl, 4H-pyranyl, morpholinyl, thiopholinyl, piperidinyl, 1,4-dithianyl, and 1,4-dioxane.

The term "hydroxy" is defined as -OH.

The term "alkoxy" is defined as -OR, wherein R is alkyl.

The term "alkoxyalkyl" is defined as an alkyl group wherein a hydrogen has been replaced by an alkoxy group. The term "(alkylthio)alkyl" is defined similarly as alkoxyalkyl, except a sulfur atom, rather than an oxygen atom, is present.

The term "hydroxyalkyl" is defined as a hydroxy group appended to an alkyl group.

The term "amino" is defined as $-NH_2$, and the term "alkylamino" is defined as $-NR_2$, wherein at least one R is alkyl and the second R is alkyl or hydrogen.

The term "acylamino" is defined as RC(=O)N, wherein R is alkyl or aryl.

The term "alkylthio" is defined as -SR, wherein R is alkyl.

The term "alkylsulfinyl" is defined as $R-SO_2$, wherein R is alkyl.

The term "alkylsulfonyl" is defined as $R-SO_3$, wherein R is alkyl.

The term "nitro" is defined as $-NO_2$.

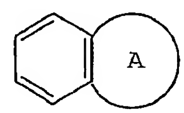
The term "trifluoromethyl" is defined as $-CF_3$.

The term "trifluoromethoxy" is defined as $-OCF_3$.

The term "cyano" is defined as -CN.

In a preferred embodiment, q is 0, or R^0 is selected from the group consisting of halo and C_{1-3}alkyl.

In a preferred group of compounds of formula (I), R^2 is represented by



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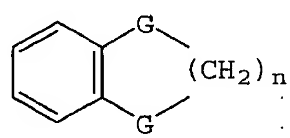
wherein the bicyclic ring can represent, for example, naphthalene or indene, or a heterocycle, such as benzoxazole, benzothiazole, benzisoxazole, benzimidazole, quinoline, indole, benzothiophene, or benzofuran, or



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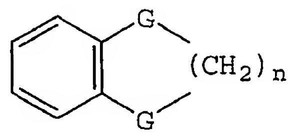
wherein n is an integer 1 or 2, and G, independently, is $C(R^a)_2$, O, S, or NR^a. The bicyclic ring comprising the R^2 substituent typically is attached to the rest of the molecule by a phenyl ring carbon atom.

In another preferred group of compounds of formula (I), R^2 is represented by an optionally substituted bicyclic ring



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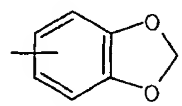
wherein n is 1 or 2, and G, independently, are $C(R^a)_2$ or O. Especially preferred R^2 substituents include



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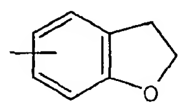

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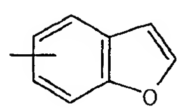

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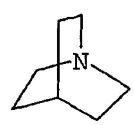
Within this particular group of compounds, nonlimiting examples of substituents for the bicyclic ring include halo (e.g., chloro), C_{1-3}alkyl (e.g., methyl, ethyl, or i-propyl), OR^a (e.g., methoxy, ethoxy, or hydroxy), CO_2R^a, halomethyl or halomethoxy (e.g., trifluoromethyl or trifluoromethoxy), cyano, nitro, and NR^aR^b.

In a preferred embodiment, R^4 is selected from the group consisting of C_{1-6}alkyl, aryl, heteroaryl, $C(=O)R^a$, $SO_2NR^aR^b$, $C(=O)OR^a$, C_{1-4}alkyleneHet, C_{1-4}alkyleneheteroaryl, C_{1-4}alkylenearyl, C_{1-4}alkylene-$C(=O)C_{1-4}$alkylenearyl, C_{1-4}alkylene$C(=O)OR^a$, C_{1-4}alkyl-ene$C(=O)NR^aR^b$, C_{1-4}alkylene$C(=O)$Het, C_{1-4}alkyleneNR^aR^b, C_{1-4}alkyleneOR^a and C_{1-4}alkylene$NR^aC(=O)R^a$.

In more preferred embodiments, R^4 is selected from the group consisting of C_{1-6}alkyl, $C(=O)R^a$, $SO_2NR^aR^b$, and C_{1-4}alkyleneHet, wherein Het is selected from the group consisting of piperazinyl, morpholinyl, pyrrolidinyl, pyrrolidonyl, tetrahydrofuran, piperidinyl,



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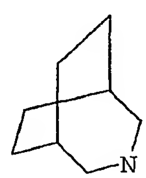
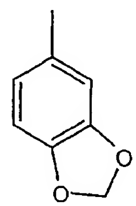


;

C_{1-4}alkyleneC_6H_5, optionally substituted with one to three groups selected from the group consisting of $C(=O)OR^a$, NR^aR^b, $NR^aSO_2CF_3$, $SO_2NR^aR^b$, CN, OR^a, $C(=O)R^a$, C_{1-4}alkyleneNR^aR^b, nitro, OC_{1-4}alkylenearyl, and OC_{1-4}alkyleneNR^aR^b; C_{1-4}alkyleneOR^a; C_{1-4}alkylene$C(=O)$-NR^aR^b; C_{1-4}alkylene$C(=O)NR^aR^c$; C_6H_5; C_{1-4}alkyleneNR^aR^b; and C_{1-4}alkylene$NHC(=O)R^a$.

In especially preferred embodiments, q is 0 or R^0 is selected from the group consisting of halo and methyl; R^1 is selected from the group consisting of hydro, C_{1-6}alkyl, and haloC_{1-6}alkyl; R^2 is selected from the group consisting of



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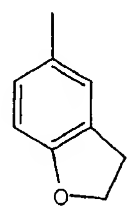

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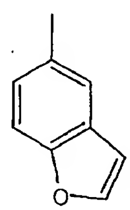
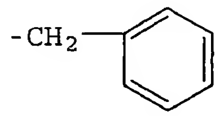
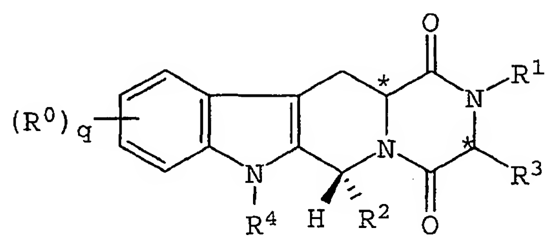


R^3 is C_{1-6}alkyl; and R^4 is selected from the group consisting of CH_3, $(CH_2)_4C(=O)OH$, $C(=O)OCH_3$, $C(=O)CH_3$, $CH_2NHCH_2C_6H_5$, CH_2NH_2, CHO, C_2H_5, $CH(CH_3)_2$, CH_2OH, $SO_2N(CH_3)_2$, and



An especially preferred subclass of compounds within the general scope of formula (I) is represented by compounds of formula (II)



(II) ,

and pharmaceutically acceptable salts and solvates (e.g., hydrates) thereof.

Compounds of formula (I) can contain one or more asymmetric center, and, therefore, can exist as stereoisomers. The present invention includes both mixtures and separate individual stereoisomers of the compounds of formula (I). Compounds of formula (I) also can exist in tautomeric forms, and the invention includes both mixtures and separate individual tautomers thereof.

Pharmaceutically acceptable salts of the compounds of formula (I) can be acid addition salts formed with pharmaceutically acceptable acids. Examples of suitable salts include, but are not

limited to, the hydrochloride, hydrobromide, sulfate, bisulfate, phosphate, hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulfonate, benzenesulfonate, and p-toluenesulfonate salts. The compounds of formula (I) also can provide pharmaceutically acceptable metal salts, in particular alkali metal salts and alkaline earth metal salts, with bases. Examples include the sodium, potassium, magnesium, and calcium salts.

Compounds of the present invention are potent and selective inhibitors of cGMP-specific PDE5. Thus, compounds of formula (I) are of interest for use in therapy, specifically for the treatment of a variety of conditions where selective inhibition of PDE5 is considered to be beneficial.

Phosphodiesterases (PDEs) catalyze the hydrolysis of cyclic nucleotides, such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). The PDEs have been classified into at least seven isoenzyme families and are present in many tissues (J.A. Beavo, *Physiol. Rev.*, *75*, p. 725 (1995)).

PDE5 inhibition is a particularly attractive target. A potent and selective inhibitor of PDE5 provides vasodilating, relaxing, and diuretic effects, all of which are beneficial in the treatment of various disease states. Research in this area has led to several classes of inhibitors based on the cGMP basic structure (E. Sybertz et al., *Expert. Opin. Ther. Pat.*, *7*, p. 631 (1997)).

The biochemical, physiological, and clinical effects of PDE5 inhibitors therefore suggest

their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, inflammatory, and/or endocrine function is desirable. The compounds of formula (I), therefore, have utility in the treatment of a number of disorders, including stable, unstable, and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, chronic obstructive pulmonary disease, malignant hypertension, pheochromocytoma, acute respiratory distress syndrome, congestive heart failure, acute and chronic renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g., postpercutaneous transluminal coronary or carotid angioplasty, or post-bypass surgery graft stenosis), peripheral vascular disease, vascular disorders, such as Raynaud's disease, thrombocythemia, inflammatory diseases, myocardial infarction, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, osteoporosis, preterm labor, benign prostatic hypertrophy, peptic ulcer, male erectile dysfunction, female sexual dysfunction, and diseases characterized by disorders of gut motility (e.g., irritable bowel syndrome).

An especially important use is the treatment of male erectile dysfunction, which is one form of impotence and is a common medical problem. Impotence can be defined as a lack of power, in the male, to copulate, and can involve an inability to achieve penile erection or ejaculation, or both. The incidence of erectile dysfunction increases with age, with about 50% of men over the age of 40 suffering from some degree of erectile dysfunction.

In addition, a further important use is the treatment of female arousal disorder, also termed female sexual arousal disorder. Female arousal disorders are defined as a recurrent inability to attain or maintain an adequate lubrication/swelling response of sexual excitement until completion of sexual activity. The arousal response consists of vasocongestion in the pelvis, vaginal lubrication, and expansion and swelling of external genitalia.

It is envisioned, therefore, that compounds of formula (I) are useful in the treatment of male erectile dysfunction and female arousal disorder. Thus, the present invention concerns the use of compounds of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal and arousal disorder in a female animal, including humans.

The term "treatment" includes preventing, lowering, stopping, or reversing the progression or severity of the condition or symptoms being treated. As such, the term "treatment" includes both medical therapeutic and/or prophylactic administration, as appropriate.

It also is understood that "a compound of formula (I)," or a physiologically acceptable salt or solvate thereof, can be administered as the neat compound, or as a pharmaceutical composition containing either entity.

Although the compounds of the invention are envisioned primarily for the treatment of sexual dysfunction in humans, such as male erectile dysfunction and female arousal disorder, they also can be used for the treatment of other disease states.

A further aspect of the present invention, therefore, is providing a compound of formula (I) for use in the treatment of stable, unstable, and variant (Prinzmetal) angina, hypertension, malignant hypertension, pheochromocytoma, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, acute respiratory distress syndrome, acute and chronic renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g., post-PTCA or post-bypass graft stenosis), peripheral vascular disease, vascular disorders such as Raynaud's disease, thrombocythemia, inflammatory diseases, prophylaxis of myocardial infarction, prophylaxis of stroke, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, osteoporosis, preterm labor, benign prostatic hypertrophy, male and female erectile dysfunction, or diseases characterized by disorders of gut motility (e.g., IBS).

According to another aspect of the present invention, there is provided the use of a compound of formula (I) for the manufacture of a medicament for the treatment of the above-noted conditions and disorders.

In a further aspect, the present invention provides a method of treating the above-noted conditions and disorders in a human or nonhuman animal body which comprises administering to said body a

therapeutically effective amount of a compound of formula (I).

Compounds of the invention can be administered by any suitable route, for example by oral, buccal, inhalation, sublingual, rectal, vaginal, transurethral, nasal, topical, percutaneous, i.e., transdermal, or parenteral (including intravenous, intramuscular, subcutaneous, and intracoronary) administration. Parenteral administration can be accomplished using a needle and syringe, or using a high pressure technique, like POWDERJECT™.

Oral administration of a compound of the invention is the preferred route. Oral administration is the most convenient and avoids the disadvantages associated with other routes of administration. For patients suffering from a swallowing disorder or from impairment of drug absorption after oral administration, the drug can be administered parenterally, e.g., sublingually or buccally.

Compounds and pharmaceutical compositions suitable for use in the present invention include those wherein the active ingredient is administered in an effective amount to achieve its intended purpose. More specifically, a "therapeutically effective amount" means an amount effective to prevent development of, or to alleviate the existing symptoms of, the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

A "therapeutically effective dose" refers to that amount of the compound that results in achieving the desired effect. Toxicity and thera-

peutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, which is expressed as the ratio between LD_{50} and ED_{50}. Compounds which exhibit high therapeutic indices are preferred. The data obtained from such data can be used in formulating a range of dosage for use in humans. The dosage of such compounds preferably lies within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed, and the route of administration utilized.

The exact formulation, route of administration, and dosage can be chosen by the individual physician in view of the patient's condition. Dosage amount and interval can be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the therapeutic effects.

The amount of composition administered is dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician.

Specifically, for administration to a human in the curative or prophylactic treatment of the conditions and disorders identified above, oral dosages of a compound of formula (I) generally are about 0.5 to about 1000 mg daily for an average

adult patient (70 kg). Thus, for a typical adult patient, individual tablets or capsules contain 0.2 to 500 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal, or sublingual administration typically are 0.1 to 500 mg per single dose as required. In practice, the physician determines the actual dosing regimen which is most suitable for an individual patient, and the dosage varies with the age, weight, and response of the particular patient. The above dosages are exemplary of the average case, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this invention.

For human use, a compound of the formula (I) can be administered alone, but generally is administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Pharmaceutical compositions for use in accordance with the present invention thus can be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries that facilitate processing of compounds of formula (I) into preparations which can be used pharmaceutically.

These pharmaceutical compositions can be manufactured in a conventional manner, e.g., by conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Proper

formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of a compound of the present invention is administered orally, the composition typically is in the form of a tablet, capsule, powder, solution, or elixir. When administered in tablet form, the composition can additionally contain a solid carrier, such as a gelatin or an adjuvant. The tablet, capsule, and powder contain about 5% to about 95% compound of the present invention, and preferably from about 25% to about 90% compound of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, or oils of animal or plant origin can be added. The liquid form of the composition can further contain physiological saline solution, dextrose or other saccharide solutions, or glycols. When administered in liquid form, the composition contains about 0.5% to about 90% by weight of a compound of the present invention, and preferably about 1% to about 50% of a compound of the present invention.

When a therapeutically effective amount of a compound of the present invention is administered by intravenous, cutaneous, or subcutaneous injection, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred composition for intravenous, cutaneous, or subcutaneous injection typically contains, in addition to a compound of the present invention, an isotonic vehicle.

For oral administration, the compounds can be formulated readily by combining a compound of formula (I) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the present compounds to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by adding a compound of formula (I) with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers and cellulose preparations. If desired, disintegrating agents can be added.

For administration by inhalation, compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin, for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds can be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampules or in multidose containers, with an added preservative. The compositions can

take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils or synthetic fatty acid esters. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension. Optionally, the suspension also can contain suitable stabilizers or agents that increase the solubility of the compounds and allow for the preparation of highly concentrated solutions. Alternatively, a present composition can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

Compounds of the present invention also can be formulated in rectal compositions, such as suppositories or retention enemas, e.g., containing conventional suppository bases. In addition to the formulations described previously, the compounds also can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion

exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Many of the compounds of the present invention can be provided as salts with pharmaceutically compatible counterions. Such pharmaceutically acceptable base addition salts are those salts that retain the biological effectiveness and properties of the free acids, and that are obtained by reaction with suitable inorganic or organic bases.

In particular, a compound of formula (I) can be administered orally, buccally, or sublingually in the form of tablets containing excipients, such as starch or lactose, or in capsules or ovules, either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations can be prepared with pharmaceutically acceptable additives, such as suspending agents. A compound also can be injected parenterally, for example, intravenously, intramuscularly, subcutaneously, or intracoronarily. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which can contain other substances, for example, salts, or monosaccharides, such as mannitol or glucose, to make the solution isotonic with blood.

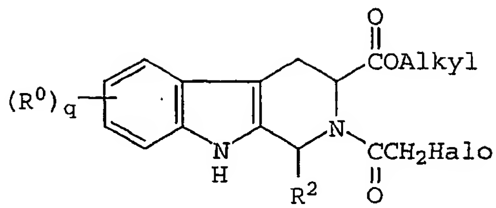
For veterinary use, a compound of formula (I) or a nontoxic salt thereof, is administered as a suitably acceptable formulation in accordance with normal veterinary practice. The veterinarian can readily determine the dosing regimen and route of administration that is most appropriate for a particular animal.

Thus, the invention provides in a further aspect a pharmaceutical composition comprising a compound of the formula (I), together with a pharmaceutically acceptable diluent or carrier therefor. There is further provided by the present invention a process of preparing a pharmaceutical composition comprising a compound of formula (I), which process comprises mixing a compound of formula (I), together with a pharmaceutically acceptable diluent or carrier therefor.

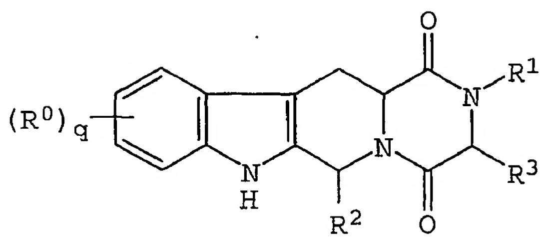
In a particular embodiment, the invention includes a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, or arousal disorder in a female animal, including humans, comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

Compounds of formula (I) can be prepared by any suitable method known in the art, or by the following processes which form part of the present invention. In the methods below, R^0, R^1, R^2, R^3, and R^4, are defined as in structural formula (I) above. In particular, compounds of structural formula (I) can be prepared according to the following synthetic schemes.

Several methods exist for synthesizing β-carbolines. For example, Daugan U.S. Patent No. 5,859,006, incorporated herein by reference, discloses preparation of compounds of structural formulae (III) and (IV):



(III)



(IV)

The compounds of structural formula (I) can be prepared in an analogous manner as a compound of structural formula (IV) using appropriately substituted starting materials.

Alternatively, a compound of structural formula (IV) can be prepared, then the indole nitrogen can be directly alkylated or acylated to provide the desired R^4 substituent. Preparation of N-substituted indoles are well known to persons skilled in the art.

It should be understood that protecting groups can be utilized in accordance with general principles of synthetic organic chemistry to provide

compounds of structural formula (I). Protecting group-forming reagents, like benzyl chloroformate and trichloroethyl chloroformate, are well known to persons skilled in the art, for example, see T.W. Greene et al., "Protective Groups in Organic Synthesis, Third Edition," John Wiley and Sons, Inc., NY, NY (1999). These protecting groups are removed when necessary by appropriate basic, acidic, or hydrogenolytic conditions known to persons skilled in the art. Accordingly, compounds of structural formula (I) not specifically exemplified herein can be prepared by persons skilled in the art.

In addition, compounds of formula (I) can be converted to other compounds of formula (I), or a compound of structural formula (IV) can be converted to a compound of structural formula (I). Thus, for example, a particular R substituent can be interconverted to prepare another suitably substituted compound of formula (I). Examples of appropriate interconversions include, but are not limited to, OR^a to hydroxy by suitable means (e.g., using an agent such as $SnCl_2$ or a palladium catalyst, like palladium-on-carbon), or amino to substituted amino, such as acylamino or sulphonylamino, using standard acylating or sulfonylating conditions. Other interconversions include indole N-H to indole $N\text{-}R^4$, nitro to amino, and cyano to $C(=O)OR^a$ or $C(=O)NR^aR^b$.

Compounds of formula (I) can be prepared by the method above as individual stereoisomers or as a racemic mixture. Individual stereoisomers of the compounds of the invention can be prepared from racemates by resolution using methods known in the art for the separation of racemic mixtures into

their constituent stereoisomers, for example, using HPLC on a chiral column, such as Hypersil naphthyl urea, or using separation of salts of stereoisomers. Compounds of the invention can be isolated in association with solvent molecules by crystallization from, or evaporation of, an appropriate solvent.

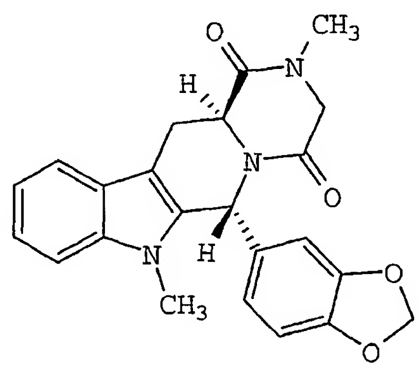
The pharmaceutically acceptable acid addition salts of the compounds of formula (I) that contain a basic center can be prepared in a conventional manner. For example, a solution of the free base can be treated with a suitable acid, either neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of formula (I) with a suitable base. Both types of salt can be formed or interconverted using ion-exchange resin techniques. Thus, according to a further aspect of the invention, a method for preparing a compound of formula (I) or a salt or solvate (e.g., hydrate) is provided, followed by (i) salt formation, or (ii) solvate (e.g., hydrate) formation.

The following additional abbreviations are used hereafter in the accompanying examples: rt (room temperature), min (minute), h (hour), g (gram), mmol (millimole), m.p. (melting point), eq (equivalents), L (liter), mL (milliliter), μL (microliter), DMSO (dimethyl sulfoxide), CH_2Cl_2 (dichloromethane), IPA (isopropyl alcohol), MeOH (methanol), DMF (dimethylformamide), Ac_2O (acetic anhy-

dride), Et_3N (triethylamine), $MeNH_2$ (methylamine), sat. (saturated), CH_3I (methyl iodide), NaH (sodium hydride), NH_4Cl (ammonium chloride), Na_2SO_4 (sodium sulfate), EtOAc (ethyl acetate), $SOCl_2$ (thionyl chloride), Et_2O (diethyl ether), $CHCl_3$ (chloroform), $NaHSO_4$ (sodium bisulfate), $NaHCO_3$ (sodium bicarbonate), HCl (hydrochloric acid), NaCl (sodium chloride), and THF (tetrahydrofuran).

Example 1

(6R,12aS)-6-Benzo[1,3]dioxol-5-yl-2,7-dimethyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]-pyrido[3,4-b]indole-1,4-dione



Example 1 was prepared in one step from compound (IV) by alkylation with methyl iodide. Under basic reaction conditions, compound (IV) was completely epimerized at the C12a position.

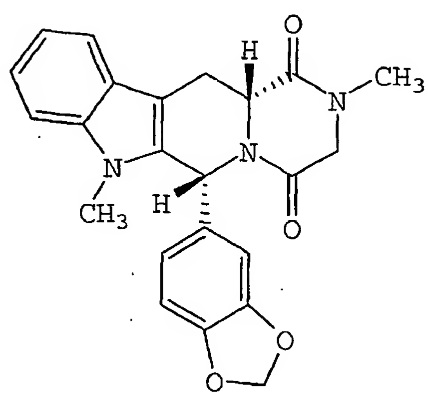
$$\text{Compound (IV)} \xrightarrow[\text{2) } CH_3I,\ 5^{\circ}C]{\text{1) NaH, THF, } 0\ ^{\circ}C} \text{Example 1}$$

A solution of compound (IV) (1.95 g, 5.0 mmol) in THF (60 mL) (prepared by dissolving compound (IV) in hot THF and cooled to room temperature) was added to a slurry of NaH (80% in mineral oil, 260 mg, 9.1 mmol) in THF (10 mL) at 0°C under a nitrogen blanket over a period of 3 minutes. The mixture was stirred at 0°C for 30 minutes after which CH_3I (0.44 mL, 7.0 mmol) was added dropwise. The resulting mixture was stirred at 5°C for an additional 30 minutes after which the mixture was diluted with CH_2Cl_2 (200 mL). The organic layer was washed successively with sat. NH_4Cl (50 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure to provide a yellow solid. The residue was dissolved in a boiling mixture of CH_2Cl_2 (15 mL), THF (30 mL), and methyl *tert*-butyl ether (20 mL), then the solution was filtered under vacuum while hot. The solid precipitate from the filtrate was collected by vacuum filtration and dried in a vacuum oven at 70°C overnight to provide Example 1 as a white solid (1.62 g, 80%): mp 386-387°C; TLC R_f (4:1 CH_2Cl_2/-EtOAc)=0.22. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.53 (d, J=7.7 Hz, 1H), 7.38-7.08 (m, 3H), 7.02 (s, 1H), 6.80 (s, 1H), 6.75-6.58 (m, 2H), 5.93 (s, 2H), 4.32 (dd, J=11.9, 4.2 Hz, 1H), 4.13 (d, J=17.7 Hz, 1H), 3.98 (d, J=17.7 Hz, 1H), 3.54 (dd, J=15.6, 4.3 Hz, 1H), 3.41 (s, 3H), 3.12-2.87 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.5, 161.3, 148.2, 148.0, 137.3, 131.6, 131.1, 125.9, 122.2, 119.6, 118.4, 109.1, 108.9, 108.3, 107.6, 101.3, 52.0, 51.4, 50.9, 33.3, 29.9, 27.5 ppm; API MS m/z 404 $[C_{23}H_{21}N_3O_4+H]^+$; $[\alpha]_D^{22°C}$=-346.0° (c=1.0, DMSO). Anal. Calcd. for

$C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N, 10.42. Found: C, 68.12, H, 5.56; N, 10.05. The relative stereochemistry of Example 1 was confirmed to be the *trans* isomer by a series of NOE difference experiments (DMSO-d_6): no NOE enhancement from the C12a proton at 4.16 ppm to the C6 proton at 6.98 ppm; no NOE enhancement from the C6 proton at 6.98 ppm to the C6 proton at 4.16 ppm. The absolute stereochemistry of Example 1 was confirmed by an empirical circular dichroism experiment.

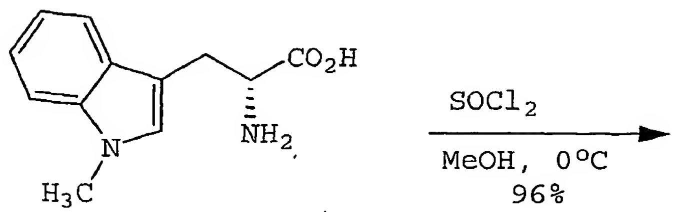
Example 2

(6R,12aR)-6-Benzo[1,3]dioxol-5-yl-2,7-dimethyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]-pyrido[3,4-b]indole-1,4-dione

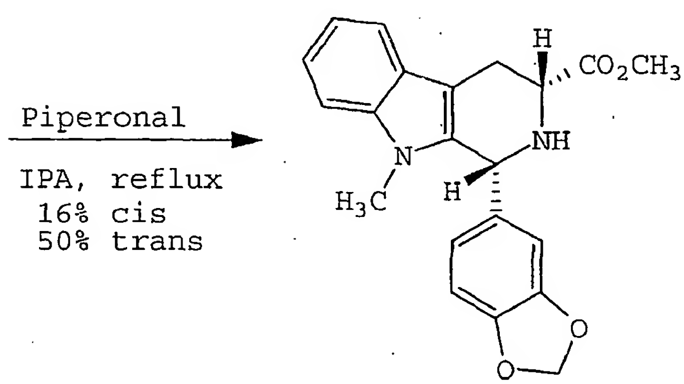


Example 2 was prepared from 1-methyl-D-tryptophan as depicted in the following synthetic Scheme 2.

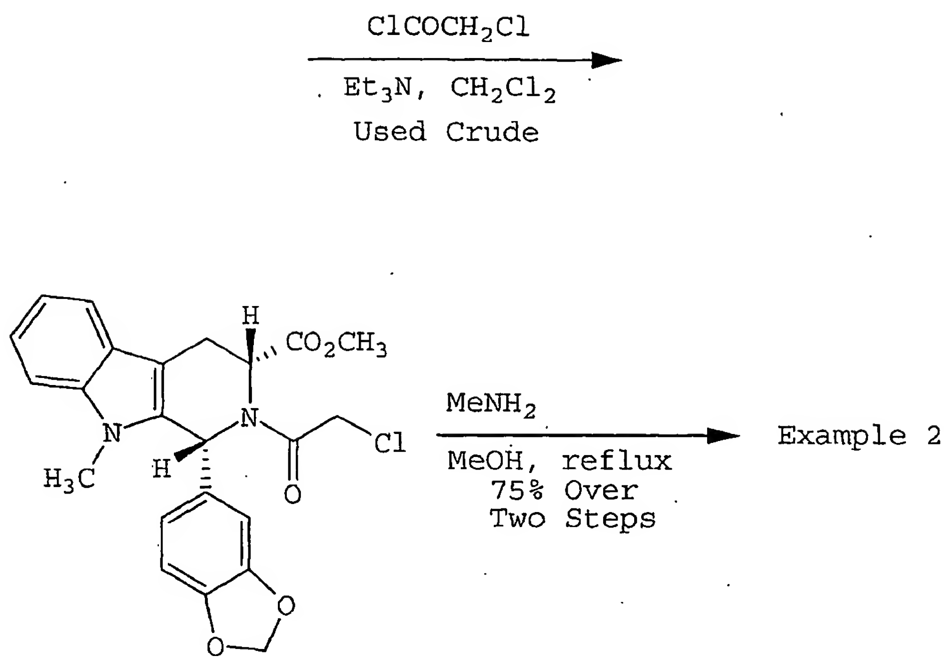
Scheme 2



Intermediate 1



Intermediate 2



Preparation of 1-Methyl-D-tryptophan methyl <u>ester hydrochloride (Intermediate 1)</u>

Thionyl chloride (1.3 mL, 18.4 mmol) was added dropwise to a suspension of 1-methyl-D-tryptophan (2.0 g, 9.2 mmol) in MeOH (30 mL) at 0°C under a nitrogen blanket. The resulting mixture was warmed slowly to room temperature and stirred for a total of 20 hours. The solvent was removed under reduced pressure and triturated with Et_2O (20 mL). The solids were collected by vacuum filtration, then dried in a vacuum oven at 60°C for 3 days to provide Intermediate 1 as an off-white powder, which was used without further purification (2.4 g, 96%): TLC R_f (1:2 EtOAc/$CHCl_3$)=0.22.

Preparation of cis-β-Carboline Intermediate 2

A suspension of Intermediate 1 (2.4 g, 8.9 mmol) and piperonal (1.5 g, 9.8 mmol) in IPA (25 mL) was stirred at reflux under a nitrogen blanket for 4 hours. The cooled mixture was diluted with IPA (20 mL), then the solid was removed by vacuum filtration. The filtrate was concentrated to afford a brown oil, which was purified by flash column chromatography, eluting with EtOAc/CH_2Cl_2 (1:9), to provide the Intermediate 2 as a white solid, but not characterized (0.50 g, 16%): TLC R_f (1:2 EtOAc/-CH_2Cl_2)=0.84. The *trans* carboline also was obtained as a white solid, but not characterized (1.6 g, 50%): TLC R_f (1:2)=0.76.

Preparation of cis-Chloroacetyl-β-carboline Intermediate 3

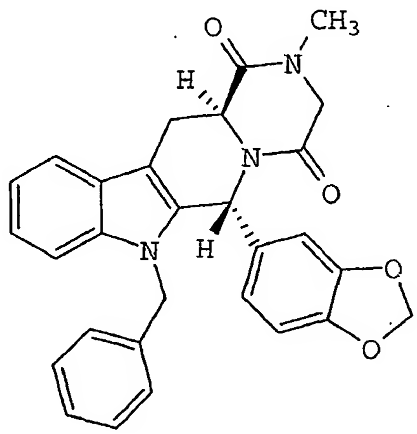
Chloroacetyl chloride (0.13 mL, 1.6 mmol) was added dropwise to a solution of Intermediate 2 (0.44 g, 1.2 mmol) and Et_3N (0.22 mL, 1.6 mmol) in CH_2Cl_2 (20 mL) at 0°C under a nitrogen blanket. The mixture was slowly warmed to room temperature and stirred for 16 hours. The resulting white suspension was diluted with CH_2Cl_2 (100 mL), washed with brine (100 mL), dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure to provide Intermediate 3 as a yellow foam, which was used without further purification (0.47 g): TLC R_f (1:2 EtOAc/$CHCl_2$)=0.91.

Preparation of Example 2

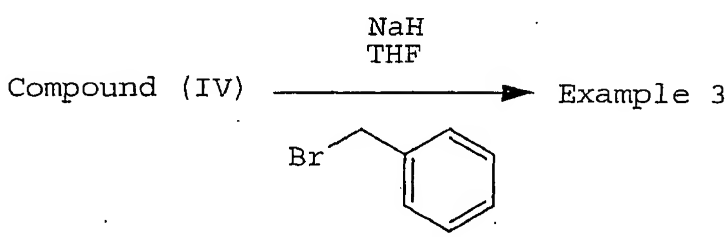
A mixture of crude Intermediate 3 (0.46 g, 1.0 mmol) and CH_3NH_2 (2.5 mL, 0.5 mmol, 2.0 M in THF) in CH_3OH (20 mL) was heated at reflux under a nitrogen blanket for 18 hours, after which the resulting orange solution was cooled to room temperature. The solvent was removed under reduced pressure to provide a brown oil. This residue was purified by flash column chromatography, eluting with EtOAc/$CHCl_3$ (1:3), to provide Example 2 as an amber powder (0.3 g, 75% over two steps): mp 228-231°C; TLC R_f (1:3 EtOAc/$CHCl_3$)=0.41. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.68 (d, J=7.9 Hz, 1H), 7.08-7.13 (m, 3H), 7.85 (d, J=8.1 Hz, 1H), 7.80 (s, 1H), 6.75 (d, J=8.1 Hz, 1H), 6.30 (s, 1H), 5.89 (s, 1H), 5.87 (s, 1H), 4.27-4.21 (m, 1H), 4.12 (d, J=17.4 Hz, 1H), 3.91 (d, J=17.4 Hz, 1H), 3.80-3.75 (m, 1H), 3.30-3.24 (m, 1H), 3.03 (s, 3H); API MS m/z 404 $(C_{23}H_{21}N_3O_4+H)^+$; $[\alpha]_D^{25°C}$=+10.0° (c=1.0, $CHCl_3$). Anal. Calcd. for $C_{23}H_{21}N_3O_4$: C, 66.98; H, 5.38; N, 10.19. Found: C, 67.26; H, 5.38; N, 9.83. The stereochemistry of Example 2 was confirmed to be the desired *cis* isomer by a series of NOE difference experiments: a positive NOE enhancement from the C12a proton at 4.24 ppm to the C6 proton at 6.30 ppm; a positive NOE enhancement from the C6 proton at 6.30 ppm to the C12a proton at 4.24 ppm.

Example 3

(6R,12aS)-6-Benzo[1,3]dioxol-5-yl-7-benzyl-2-methyl-2,3,6,7,12,12a-hexahydropyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione



Example 3 was prepared in one step from compound (IV) by alkylation with benzyl bromide. Like Example 1, the basic reaction conditions resulted in complete epimerization of compound (IV).

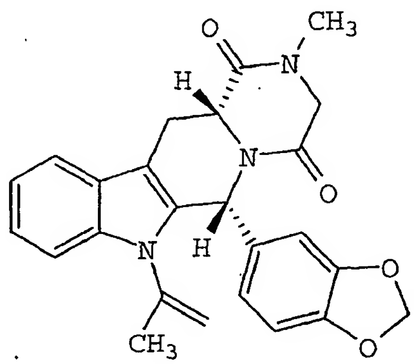


A dried flask under a nitrogen blanket was charged with 2.05 g (5.26 mmol) of compound (IV) and dry THF, then cooled to 0°C with stirring. NaH (0.32 g, 7.9 mmol) was added as a 60% oil dispersion

in several portions. The reaction mixture was allowed to warm to ambient temperature over 15 minutes, then 0.69 ml (5.8 mmol) benzyl bromide was added. After 20 hours, the reaction mixture was diluted with EtOAc, washed with 3% $NaHSO_4$, sat. $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and the solvent stripped on a rotavapor. The resulting oil was purified by flash chromatography (4.8 x 23 cm, CH_2Cl_2/EtOAc/MeOH (90:10:1) to yield after drying *in vacuo* 2.14 g (85% yield) of a white amorphous solid: mp 110-145°C. ^1H NMR (DMSO-d_6) δ: 7.59 (d, J=7.6, 1H), 7.40 (d, J=7.9, 1H), 7.26-7.07 (m, 5H), 6.88-6.80 (m, 4H), 6.71 (s, 1H), 6.58 (d, J=8.0, 1H), 6.00 (d, J=10.8, 2H), 5.36 (d, J=16.8, 1H), 4.75 (d, J=16.8, 1H), 4.23 (d, J=17.6, 1H), 4.12 (d of d, J_1=11.7, J_2=4.0, 1H), 3.99 (d, J=17.6, 1H), 3.35 (d of d, J_1=14.1, J_2 obscured by water peak, 1H), 3.01 (d of d, J_1=12.1, J_2=15.1, 1H), 2.83 (s, 3H); TLC R_f (CH_2Cl_2/EtOAc/MeOH) (90:10:1)=0.31; MS m/z 502 (M+Na); $[\alpha]_D^{25°C}$=-230.2 (c=0.1, DMSO); Anal. Calcd. for $C_{29}H_{25}N_3O_4$: C, 72.64; H, 5.25; N, 8.76. Found: C, 72.46; H, 5.40; N, 8.42. Trans stereochemistry was confirmed by HMQC and NOE experiments: HMQC assigns 6.80 ppm singlet to C6 proton; positive NOE enhancement observed from C12a (4.12 ppm) to pendent aryl protons at 6.58 ppm and 6.71 ppm and not to C6, and no NOE observed from C6 to C12a.

Example 4

(6R,12aR)-7-Acetyl-6-benzo[1,3]dioxol-5-yl-2-methyl-2,3,6,7,12,12a-hexahydropyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione



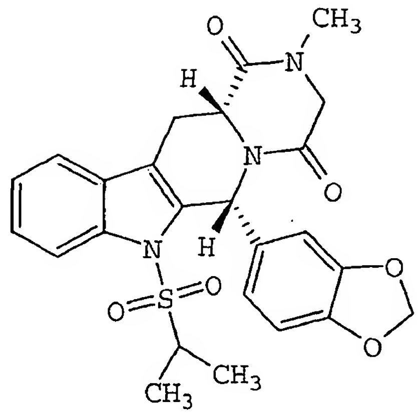
Example 4 was prepared by aceylating compound (IV) using acetic anhydride.

$$\text{Compound (IV)} \xrightarrow[\text{THF}]{\text{Ac}_2\text{O, 4-DMAP}} \text{Example 4}$$

Compound (IV) (2.01 g, 5.16 mmol), 4-dimethylaminopyridine (0.946 g, 7.74 mmol), and Ac_2O (0.97 ml, 10 mmol) were slurried in THF in a dry flask under a nitrogen blanket and stirred magnetically. The reaction was monitored by TLC. After 24 hours, an additional 0.97 ml Ac_2O was added. After 7 days, the reaction was quenched by dilution with EtOAc, and aqueous work-up (washed with sat. $NaHCO_3$, 1 N HCl, and sat. NaCl, dried over Na_2SO_4, filtered, and stripped on a rotavapor). The residue was puri-

fied by flash chromatography (4.8 x 22 cm, CH_2Cl_2/-EtOAc/MeOH) (90:10:1) to yield after drying *in vacuo* 1.87 g (84%) of a white amorphous solid: mp 145-159°C. ^1H NMR (DMSO-d_6) δ: 7.85 (d, J=6.8, 1H), 7.78 (d, J=6.8, 1H), 7.37-7.33 (m, 2H), 7.09 (s, 1H), 6.78 (s, 1H), 6.71 (d, J=8.1, 1H), 6.64 (d, J=8.1, 1H), 5.92 (d, J=4.4, 2H), 4.42 (d of d, J_1=11.7, J_2=4.5, 1H), 4.21 (d, J=17.0, 1H), 3.93 (d, J=17.1, 1H), 3.55 (d of d, J_1=16.4, J_2=4.7, 1H), 2.96 (d of d, J_1=16.4, J_2=12.6, 1H), 2.90 (s, 3H), 2.71 (s, 3H); TLC R_f (CH_2Cl_2/EtOAc/MeOH) (90:10:1)=0.22; MS m/z 454 (M+Na); Anal. Calcd. for $C_{24}H_{21}N_3O_5$, 0.33 H_2O: C, 65.91; H, 4.99; N, 9.61. Found: C, 65.95; H, 4.75; N, 9.64. Cis stereochemistry was confirmed by NOE experiments: Positive NOE enhancements observed from C12a (4.42 ppm) to C6 (7.09 ppm) and from C6 to C12a.

Example 5



Compounds of the present invention can be formulated into tablets for oral administration. For example, a compound of formula (I) can be formed into a dispersion with a polymeric carrier by the coprecipitation method set forth in WO 96/38131, incorporated herein by reference. The coprecipitated dispersion then can be blended with excipients, then pressed into tablets, which optionally are film-coated.

The compounds of structural formula (I) were tested for an ability to inhibit PDE5. The ability of a compound to inhibit PDE5 activity is related to the IC_{50} value for the compound, i.e., the concentration of inhibitor required for 50% inhibition of enzyme activity. The IC_{50} value for compounds of structural formula (I) were determined using recombinant human PDE5.

The compounds of the present invention typically exhibit an IC_{50} value against recombinant

human PDE5 of less than about 50 μM, and preferably less than about 25 μM, and more preferably less than about 15 μm. The compounds of the present invention typically exhibit an IC_{50} value against recombinant human PDE5 of less than about 1 μM, and often less than about 0.25 μM. To achieve the full advantage of the present invention, a present PDE5 inhibitor has an IC_{50} of about 0.1 nM to about 15 μM.

The production of recombinant human PDEs and the IC_{50} determinations can be accomplished by well-known methods in the art. Exemplary methods are described as follows:

EXPRESSION OF HUMAN PDEs

Expression in *Saccharomyces cerevisiae* (Yeast)

Recombinant production of human PDE1B, PDE2, PDE4A, PDE4B, PDE4C, PDE4D, PDE5, and PDE7 was carried out similarly to that described in Example 7 of U.S. Patent No. 5,702,936, incorporated herein by reference, except that the yeast transformation vector employed, which is derived from the basic ADH2 plasmid described in Price et al., *Methods in Enzymology, 185*, pp. 308-318 (1990), incorporated yeast ADH2 promoter and terminator sequences and the Saccharomyces cerevisiae host was the protease-deficient strain BJ2-54 deposited on August 31, 1998 with the American Type Culture Collection, Manassas, Virginia, under accession number ATCC 74465. Transformed host cells were grown in 2X SC-leu medium, pH 6.2, with trace metals, and vitamins. After 24 hours, YEP medium-containing glycerol was added to a

final concentration of 2X YET/3% glycerol. Approximately 24 hr later, cells were harvested, washed, and stored at -70°C.

HUMAN PHOSPHODIESTERASE PREPARATIONS

Phosphodiesterase Activity Determinations

Phosphodiesterase activity of the preparations was determined as follows. PDE assays utilizing a charcoal separation technique were performed essentially as described in Loughney et al. (1996). In this assay, PDE activity converts [32P]cAMP or [32P]cGMP to the corresponding [32P]5'-AMP or [32P]5'-GMP in proportion to the amount of PDE activity present. The [32P]5'-AMP or [32P]5'-GMP then was quantitatively converted to free [32P]phosphate and unlabeled adenosine or guanosine by the action of snake venom 5'-nucleotidase. Hence, the amount of [32P]phosphate liberated is proportional to enzyme activity. The assay was performed at 30°C in a 100 μL reaction mixture containing (final concentrations) 40 mM Tris HCl (pH 8.0), 1 μM $ZnSO_4$, 5 mM $MgCl_2$, and 0.1 mg/mL bovine serum albumin (BSA). PDE enzyme was present in quantities that yield <30% total hydrolysis of substrate (linear assay conditions). The assay was initiated by addition of substrate (1 mM [32P]cAMP or cGMP), and the mixture was incubated for 12 minutes. Seventy-five (75) μg of Crotalus atrox venom then was added, and the incubation was continued for 3 minutes (15 minutes total). The reaction was stopped by addition of 200 μL of activated charcoal (25 mg/mL suspension in 0.1

M NaH_2PO_4, pH 4). After centrifugation (750 X g for 3 minutes) to sediment the charcoal, a sample of the supernatant was taken for radioactivity determination in a scintillation counter and the PDE activity was calculated.

Purification of PDE5 from *S. cerevisiae*

Cell pellets (29 g) were thawed on ice with an equal volume of Lysis Buffer (25 mM Tris HCl, pH 8, 5 mM $MgCl_2$, 0.25 mM DTT, 1 mM benzamidine, and 10 μM $ZnSO_4$). Cells were lysed in a Microfluidizer® (Microfluidics Corp.) using nitrogen at 20,000 psi. The lysate was centrifuged and filtered through 0.45 μm disposable filters. The filtrate was applied to a 150 mL column of Q SEPHAROSE® Fast-Flow (Pharmacia). The column was washed with 1.5 volumes of Buffer A (20 mM Bis-Tris Propane, pH 6.8, 1 mM $MgCl_2$, 0.25 mM DTT, 10 μM $ZnSO_4$) and eluted with a step gradient of 125 mM NaCl in Buffer A followed by a linear gradient of 125-1000 mM NaCl in Buffer A. Active fractions from the linear gradient were applied to a 180 mL hydroxyapatite column in Buffer B (20 mM Bis-Tris Propane (pH 6.8), 1 mM $MgCl_2$, 0.25 mM DTT, 10 μM $ZnSO_4$, and 250 mM KCl). After loading, the column was washed with 2 volumes of Buffer B and eluted with a linear gradient of 0-125 mM potassium phosphate in Buffer B. Active fractions were pooled, precipitated with 60% ammonium sulfate, and resuspended in Buffer C (20 mM Bis-Tris Propane, pH 6.8, 125 mM NaCl, 0.5 mM DTT, and 10 μM $ZnSO_4$). The pool was applied to a 140 mL column of SEPHACRYL® S-300 HR and eluted with Buffer C. Active

fractions were diluted to 50% glycerol and stored at -20°C.

The resultant preparations were about 85% pure by SDS-PAGE. These preparations had specific activities of about 3 μmol cGMP hydrolyzed per minute per milligram protein.

Inhibitory Effect on cGMP-PDE

cGMP-PDE activity of compounds of the present invention was measured using a one-step assay adapted from Wells et al., *Biochim. Biophys. Acta*, 384, 430 (1975). The reaction medium contained 50 mM Tris-HCl, pH 7.5, 5 mM magnesium acetate, 250 μg/ml 5'-Nucleotidase, 1 mM EGTA, and 0.15 μM 8-[^{3}H]-cGMP. Unless otherwise indicated, the enzyme used was a human recombinant PDE5 (ICOS Corp., Bothell, Washington).

Compounds of the invention were dissolved in DMSO finally present at 2% in the assay. The incubation time was 30 minutes during which the total substrate conversion did not exceed 30%.

The IC_{50} values for the compounds examined were determined from concentration-response curves typically using concentrations ranging from 10 nM to 10 μM. Tests against other PDE enzymes using standard methodology showed that compounds of the invention are selective for the cGMP-specific PDE enzyme.

Biological Data

The compounds according to the present invention were typically found to exhibit an IC_{50}

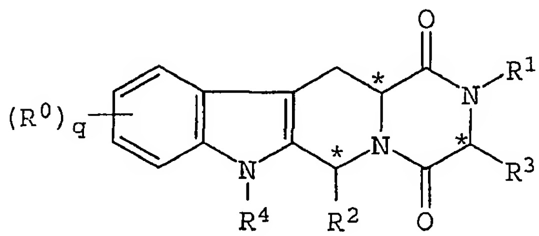
value of less than 500 nM (i.e., 0.5 μM). *In vitro* test data for representative compounds of the invention is given in the following table:

Table 1: *In vitro* Results	
Example	**PDE5 IC_{50} (μM)**
1	0.124
2	0.571
3	0.313
4	0.007

Obviously, many modifications and variations of the invention as hereinbefore set forth can be made without departing from the spirit and scope thereof, and, therefore, only such limitations should be imposed as are indicated by the appended claims.

WHAT IS CLAIMED IS:

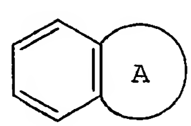
1. A compound having a formula



wherein R^0, independently, is selected from the group consisting of halo and C_{1-6}alkyl;

R^1 is selected from the group consisting of hydro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}-alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, aryl-C_{1-3}alkyl, C_{1-3}alkylenearyl, and heteroarylC_{1-3}alkyl;

R^2 is selected from the group consisting of an optionally substituted monocyclic aromatic ring selected from the group consisting of benzene, thiophene, furan, and pyridine, and an optionally substituted bicyclic ring



wherein the fused ring A is a 5- or 6-membered ring, saturated or partially or fully unsaturated, and comprises carbon atoms and optionally one or two

heteroatoms selected from oxygen, sulfur, and nitrogen;

R^3 is selected from the group consisting of hydro and C_{1-6}alkyl,

or R^1 and R^3 together form a 3- or 4-membered alkyl or alkenyl chain component of a 5- or 6-membered ring;

R^4 is selected from the group consisting of C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}heterocycloalkyl, C_{2-6}-alkenyl, C_{1-3}alkylenearyl, arylC_{1-3}alkyl, heteroaryl-C_{1-3}alkyl, $C(=O)R^a$, aryl, heteroaryl, $C(=O)OR^a$, $C(=O)$-NR^aR^b, $C(=S)NR^aR^b$, SO_2R^a, SO_2OR^a, $SO_2NR^aR^b$, $S(=O)R^a$, $S(=O)NR^aR^b$, $C(=O)NR^aC_{1-4}$alkyleneOR^a, $C(=O)NR^aC_{1-4}$alkyl-eneHet, $C(=O)C_{1-4}$alkylenearyl, $C(=O)C_{1-4}$alkyleneheteroaryl, C_{1-4}alkylenearyl substituted with one or more of $SO_2NR^aR^b$, NR^aR^b, $C(=O)OR^a$, $NR^aSO_2CF_3$, CN, NO_2, $C(=O)R^a$, OR^a, C_{1-4}alkyleneNR^{a}R^b, and OC_{1-4}alkyleneNR^{a}R^b, C_{1-4}alkyleneHet, C_{1-4}alkyleneC(=O)C_{1-4}alkylenearyl, C_{1-4}alkyleneC(=O)C_{1-4}alkyleneheteroaryl, C_{1-4}alkylene-C(=O)Het, C_{1-4}alkyleneC(=O)NR^{a}R^b, C_{1-4}alkyleneOR^a, C_{1-4}alkyleneNR^{a}C(=O)R^a, C_{1-4}alkyleneOC_{1-4}alkyleneOR^a, C_{1-4}alkyleneNR^{a}R^b, C_{1-4}alkyleneC(=O)OR^a, and C_{1-4}alkyl-eneOC_{1-4}alkyleneC(=O)OR^a;

Het represents a 5- or 6-membered heterocyclic ring, saturated or partially or fully unsaturated, containing at least one heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur, and optionally substituted with C_{1-4}alkyl or $C(=O)OR^a$;

R^a is selected from the group consisting of hydro, C_{1-6}alkyl, aryl, arylC_{1-3}alkyl, C_{1-3}alkylenearyl, heteroaryl, heteroarylC_{1-3}alkyl, and C_{1-3}alkyl-eneheteroaryl;

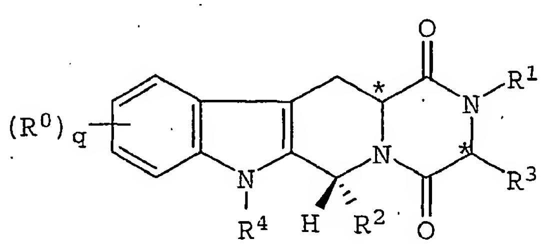
R^b is selected from the group consisting of hydro, C_{1-6}alkyl, aryl, heteroaryl, arylC_{1-3}alkyl, heteroarylC_{1-3}alkyl, C_{1-3}alkyleneN$(R^a)_2$, C_{1-3}alkylene-aryl, C_{1-3}alkyleneHet, haloC_{1-3}alkyl, C_{3-8}cycloalkyl, C_{3-8}heterocycloalkyl, C_{1-3}alkyleneheteroaryl, C_{1-3}-alkyleneC(=O)OR^a, and C_{1-3}alkyleneC_{3-8}heterocycloalkyl;

or R^a and R^b are taken together to form a 5- or 6-membered ring, optionally containing at least one heteroatom;

q is 0, 1, 2, 3, or 4; and

pharmaceutically acceptable salts and hydrates thereof.

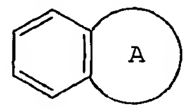
2. The compound of claim 1 represented by the formula



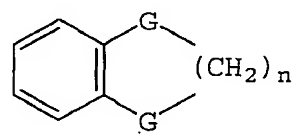
and pharmaceutically acceptable salts and hydrates thereof.

3. The compound of claim 1 wherein q is 0 or R^0 is selected from the group consisting of halo and C_{1-3}alkyl.

4. The compound of claim 1 wherein R^2 is the optionally substituted bicyclic ring



5. The compound of claim 4 wherein R^2 is



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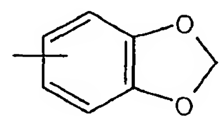
and wherein n is an integer 1 or 2, and G, independently, are $C(R^a)_2$, O, S, or NR^a.

6. The compound of claim 1 wherein R^2 is selected from the group consisting of



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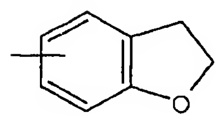

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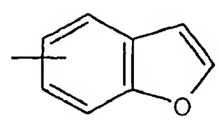

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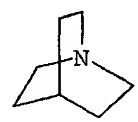
7. The compound of claim 1 wherein the R^4 group is selected from the group consisting of C_{1-6}-alkyl, $C(=O)R^a$, $C(=O)OR^a$, $SO_2NR^aR^b$, aryl, heteroaryl, C_{1-4}alkyleneHet, C_{1-4}alkyleneheteroaryl, C_{1-4}alkylene-aryl, C_{1-4}alkyleneC(=O)C_{1-4}alkylenearyl, C_{1-4}alkylene-C(=O)OR^a, C_{1-4}alkyleneC(=O)NR^aR^b, C_{1-4}alkyleneC(=O)Het, C_{1-4}alkyleneNR^aR^b, C_{1-4}alkyleneOR^a, and C_{1-4}alkylene-$NR^aC(=O)R^a$.

8. The compound of claim 7 wherein R^4 is selected from the group consisting of C_{1-6}alkyl, $C(=O)R^a$, $SO_2NR^aR^b$; C_{1-4}alkyleneHet, wherein Het is selected from the group consisting of piperazinyl, morpholinyl, pyrrolidinyl, pyrrolidonyl, tetrahydrofuran, piperidinyl,



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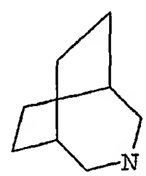

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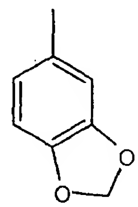
C_{1-4}alkyleneC_6H_5, optionally substituted with one to three groups selected from the group consisting of $C(=O)OR^a$, NR^aR^b, $NR^aSO_2CF_3$, $SO_2NR^aR^b$, CN, OR^a, $C(=O)R^a$, C_{1-4}alkyleneNR^aR^b, nitro, OC_{1-4}alkylenearyl, and OC_{1-4}alkyleneNR^aR^b; C_{1-4}alkyleneC(=O)benzyl; C_{1-4}alkyleneOR^a; C_{1-4}alkyleneC(=O)OR^a; C_{1-4}alkyleneC(=O)NR^aR^b; C_6H_5; C_{1-4}alkyleneNR^aR^b; and C_{1-4}alkyleneNHC(=O)R^a.

9. The compound of claim 8 wherein R^4 is selected from the group consisting of C_{1-6}alkyl, C_{1-4}-alkylenearyl, $C(=O)R^a$, and $SO_2NR^aR^b$.

10. The compound of claim 1 wherein q is 0 or R^0 is halo or methyl; R^1 is selected from the group consisting of hydrogen, C_{1-6}alkyl, and halo-C_{1-6}alkyl; R^2 is selected from the group consisting of



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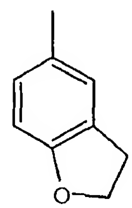

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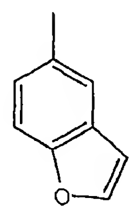


;

R^3 is C_{1-6}alkyl; and R^4 is selected from the group consisting of C_{1-6}alkyl, $C(=O)R^a$, $SO_2NR^aR^b$, C_{1-4}alkyleneаryl, C_{1-4}alkyleneC(=O)OR^a, C(=O)OR^a, C_{1-4}alkylene-NR^{a}R^b, and C_{1-4}alkyleneOR^a.

11. The compound of claim 10 wherein q is 0, R^1 is methyl, R^3 is hydro, and R^4 is selected from the group consisting of methyl, benzyl, $C(=O)CH_3$, $SO_2N(CH_3)_2$, CHO, C_2H_5, $CH(CH_3)_2$, $(CH_2)_4C(=O)OH$, $C(=O)OCH_3$, $CH_2NHCH_2C_6H_5$, CH_2NH_2, and CH_2OH.

12. The compound selected from the group consisting of

(6R,12aS)-6-benzo[1,3]dioxol-5-yl-2,7-dimethyl- 2,3,6,7,12,12a-hexahydropyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione;

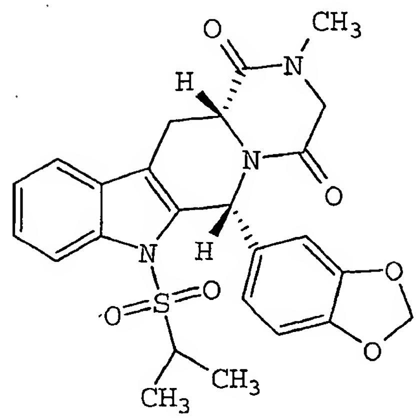
(6R,12aR)-6-benzo[1,3]dioxol-5-yl-2,7-dimethyl-2,3,6,7,12,12a-hexahydropyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione;

(6R,12aS)-6-benzo[1,3]dioxol-5-yl-7-benzyl-2-methyl-2,3,6,7,12,12a-hexahydropyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione; and

(6R,12aR)-7-acetyl-6-benzo[1,3]dioxol-5-yl-2-methyl-2,3,6,7,12,12a-hexahydropyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione;

and pharmaceutically acceptable salts and solvates thereof.

13. A compound having the formula:



14. A pharmaceutical composition comprising a compound of claim 1, together with a pharmaceutically acceptable diluent or carrier.

15. A method of treating a male or female animal in the treatment of a condition where inhibition of a cGMP-specific PDE is of a therapeutic benefit comprising treating said animal with an effective amount of a pharmaceutical composition comprising a compound of claim 1, together with a pharmaceutically acceptable diluent or carrier.

16. The method of claim 15 wherein the condition is male erectile dysfunction.

17. The method of claim 16 wherein the treatment is an oral treatment.

18. The method of claim 15 wherein the condition is female sexual arousal disorder.

19. The method of claim 18 wherein the treatment is an oral treatment.

20. The method of claim 15 wherein the condition is selected from the group consisting of stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, malignant hypertension, pheochromocytoma, acute respiratory distress syndrome, congestive heart failure, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, a peripheral vascular disease, a vascular disorder, thrombocythemia, an inflammatory disease, myocardial infarction, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic ulcer, a gut motility disorder, postpercutaneous transluminal coronary angioplasty, carotid angioplasty, postbypass surgery graft stenosis, osteoporosis, preterm labor, benign prostatic hypertrophy, and irritable bowel syndrome.

21. A method of treating a condition where inhibition of a cGMP-specific PDE is of therapeutic benefit, in a human or a nonhuman animal body, comprising administering to said body a therapeutically effective amount of a compound of claim 1.

22. A method for the curative or prophylactic treatment of male erectile dysfunction or female sexual arousal disorder, comprising administration of an effective dose of a compound of claim 1, and pharmaceutically acceptable salts and solvates thereof, to an animal.

23. Use of a compound of claim 1 for the manufacture of a medicament for the curative or prophylactic treatment of a condition where inhibition of a cGMP-specific PDE is of a therapeutic benefit.